Version with Markings to Show Changes Made

In the Specification

Page 1, paragraph 1 (AMENDED)

This application is a **[divisional]** **continuation** of U.S. Patent Application Serial No. 09/403,429, now U.S. Patent No. _____, issued _____, which was the National Phase filing of International Patent Application No. PCT/JP99/04015, filed July 27, 1999.

Page 4, paragraph 1 (AMENDED)

from the group comprising nourishing and cordial agents, antipyretic-anodyne-anti-inflammatory drugs, psychotropics, antianxiety drugs, antidepressants, hypnotic-sedative drugs, spasmolytics, central nervous system drugs, brain metabolism ameliorating agents, brain circulation ameliorating agents, antiepileptics, sympathomimetics, gastrointestinal agents, antacids, antiulcer agents, antitussive- **[expetorants]** **expectorants**, antiemetics, respiratory accelerators, bronchodilators, antiallergic drugs, dental buccal drugs, antihistamines, cardiotonics, antiarrythmic drugs, diuretics, antihypertensive agents, vasoconstrictors, coronary vasodilators, peripheral vasodilators, antihypolipidemic agents, cholagogues, antibiotics, chemotherapeutic drugs, antidiabetic agents, drugs for osteoporosis, antirheumatism agents, skeletal muscle relaxants, antivertigos, hormones, alkaloid narcotics, sulfa drugs, arthrifuges, blood coagulation inhibitors, antitumor agents, drugs for Alzheimer's disease and the like are exemplified.

Page 5, paragraph 13 (AMENDED)

As the antitussive **[expetorants]** **expectorants**, for instance, chloperastine hydrochloride,

Page 8, paragraph 7 (AMENDED)

Among the above pharmacologically active ingredients, nourishing and cordial agents, antipyretic-anodyne-anti-inflammatory drugs, hypnotic-sedative drugs, central nervous system drugs, gastrointestinal agents, antiulcer agents, antitussive- **[expetorants]** **expectorants**, antiallergic drugs, antiarrythmic drugs, diuretics, antihypertensive agents, vasoconstrictors, coronary vasodilators, antihypolipidemic agents, antidiabetic agents, drugs for osteoporosis, skeletal muscle relaxants, antivertigos and the like are exemplified.

Page 10, paragraph 5 (AMENDED)

Concretely, for example, raw material pulp such as wood pulp and cotton **[leader]** **linter** is immersed in 10 to 50% concentration of **an** aqueous solution of sodium hydroxide, and pressed to obtain the alkaline cellulose of which NaOH/cellulose ratio is 0.1 to 1.2 (ratio by weight). Next, the crude low-substituted hydroxypropylcellulose containing free

Page 11, paragraph 2 (AMENDED)

The crude low-substituted hydroxypropylcellulose containing free alkaline is dispersed in water or hot water containing 5 to 80 % of acid which is **[need]** **necessary** to neutralize the **[all]** **total** amount of alkaline, and a part of the crude low-substituted hydroxypropylcellulose containing free alkaline is dissolved therein. Further, acid is added to neutralize the **[remained]** **remaining** alkaline.

Page 13, paragraph 5 (AMENDED)

As the flavorants, for example, lemon, lemon lime, orange, **[mentol]** **menthol**, strawberry and the like are exemplified.

Page 27, paragraph 1 (AMENDED)

The **[orally]** **oral** disintegration time of the rapidly disintegrable solid preparation of the present invention (the time for healthy male or female adults to complete disintegration by buccal saliva) is usually 5 to 50 seconds, preferably 5 to 40 seconds, more preferably 5 to 35 seconds.

Page 29, paragraph 3 (AMENDED)

When manidipine hydrochloride is used as the pharmacologically active ingredient, the rapidly disintegrable solid preparation of the present invention is useful for treatment and prevention of circulatory system diseases such as hypertension, ischemic heart disease (e.g. angina **[pectori]** **pectoris**, myocardial infarction and the like), cerebral and peripheral circulatory disorders (e.g., cerebral infarction, transient ischemic attack, constriction of renal artery and the like) and the like. The dosage amount of the preparation per an adult (body weight: 60 kg) is 1 to 200 mg/day, preferably 10 to 20 mg/day, as manidipine hydrochloride. The rapidly disintegrable solid preparation is usually administered once a day after **[breakrapidly]** **breakfast**.

In the Claims

10. (AMENDED) **[A preparation of Claim 1, wherein the pharmacologically active ingredient is]**

A rapidly disintegrable solid preparation which comprises (a) manidipine hydrochloride**, (ii) a sugar and (iii) a low-substituted hydroxypropylcellulose having 5% by weight or more to less than 7% by weight of hydroxypropoxyl groups**.

11. (AMENDED) **[A preparation of Claim 1, wherein the pharmacologically active ingredient is] A rapidly disintegrable solid preparation which comprises (a)** pioglitazone hydrochloride**, (ii) a sugar and (iii) a low-substituted hydroxypropylcellulose having 5% by weight or more to less than 7% by weight of hydroxypropoxyl groups**.

12. (AMENDED) **[A preparation of Claim 1, wherein the pharmacologically active ingredient is] A rapidly disintegrable solid preparation which comprises (a)** candesartan cilexetil**, (ii) a sugar and (iii) a low-substituted hydroxypropylcellulose having 5% by weight or more to less than 7% by weight of hydroxypropoxyl groups**.

18. (AMENDED) **[Use of a low-substituted hydroxypropylcellulose having 5% by weight or more to less than 7% by weight of hydroxypropoxyl group for producing] A method for preparing** a rapidly disintegrable solid preparation comprising **combining a low-substituted hydroxypropylcellulose having 5% to less than 7% by weight of hydroxpropoxyl groups,** a pharmacologically active ingredient and a sugar.

19. (AMENDED) A method for improving fast disintegrability of a solid preparation comprising **combining** a pharmacologically active ingredient and a sugar **[which is characterized in that] with** a low-substituted hydroxypropylcellulose having 5% by weight or more to less than 7% by weight of hydroxypropoxyl **[group is contained therein] groups**.

REMARKS

I. Amendments

By this amendment, claims 10-12, 18 and 19 have been amended; and new claim 20 has been added.

Typographical and grammatical errors have also been corrected throughout the specification.

This amendment adds no new matter to the specification. Support for this amendment is found in the specification and claims as filed. Support for new claim 20 may be found *inter alia* at page 28, lines 5-7; lines 10-14 and lines 25 and 26. Claims 10-12 have been re-written as independent claims, incorporating the subject matter of independent claim 1.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version with Markings to Show Changes Made".

No amendment of inventorship is necessitated by this amendment.

II. Status of the Pending Claims

Claim 8 was cancelled in a Preliminary Amendment which was submitted on March 7, 2001, at the time of the filing of the specification. The Examiner's acknowledgement of the cancellation of this claim is respectfully requested.

III. Previously Submitted Information Disclosure Statement

Applicants submitted an Information Disclosure Statement at the time of the filing of the present application, on March 7, 2001. Four references were cited. Applicants have not yet received an Examiner-initialed copy of their Form 1449. Applicants respectfully request that the Examiner provide the initialed copy, if the references have been reviewed. Applicants respectfully request that the Examiner contact Applicants' attorney if the Form 1449 or any of the references are missing from the Examiner's file.

IV. Discussion of the Rejection under 35 U.S.C. Sec. 101 of Claims 1-8 and 13-19

Claims 1-8 and 13-19 have been provisionally rejected under 35 U.S.C. Sec. 101 as claiming the same invention as that of claims 1-7 and 13-19 of co-pending U.S. Patent Application Serial No. 09/403,429.

In the co-pending application, the pending claims are directed to a single active ingredient, lansoprazole. The present independent claims 1, 18 and 19 are directed to preparations; methods of preparing said preparations or methods of use of said preparations wherein the pharmacologically active ingredient is not specified, so the invention defined by the present claim 1 is broader than that of the co-pending application.

Claims 2-7 and 13-17 depend upon claim 1. Moreover, as noted above, in the present application, claim 8, directed to lansoprazole has already been cancelled.

Therefore as the present invention does not claim the same invention as the co-pending application, Applicants respectfully request withdrawal of the Sec. 101 rejection of claims 1-7 and 13-19.

V. Discussion of the Rejection under 35 U.S.C. Sec. 101 of Claim 18

Claim 18 has been rejected under 35 U.S.C. Sec. 101 because the claimed invention is directed to non-statutory subject matter.

By this amendment, claim 18 has been re-written to recite a process. This amendment adds no new matter to the specification. Support for the amendment may be found *inter alia* at page 22, line 27 – page 23, line 5.

Therefore, Applicants respectfully request withdrawal of the Sec. 101 rejection of Claim 18.

VI. Discussion of the Rejection under 35 U.S.C. Sec. 102(b) over Ohno *et al.*

Claims 1-7, 9 and 13-17 have been rejected under 35 U.S.C. Sec. 102(b) as anticipated by Ohno *et al.* (U.S. Patent No. 5,958,453).

The present invention is directed to a rapidly disintegrable solid preparation comprising a pharmacologically active ingredient, a sugar and a low-substituted hydroxypropylcellulose

having 5% to less than 7% of hydroxypropoxyl groups, a method for preparing a rapidly disintegrable solid preparation and a method for improving fast disintegrability of a solid preparation. Applicants do not believe that their invention as set forth in the present claims, is anticipated by the cited reference.

Ohno *et al.* is directed to solid pharmaceutical preparations. Low-substituted hydroxypropyl cellulose is mentioned generally as a disintegrant in col. 5, lines 23-24 of the cited reference. More specifically, L-HPC was utilized in Comparative Examples 3, 4 and 5. However, the cited L-HPC is different from the L-HPC presently claimed. The cited L-HPC is of higher hydroxypropoxyl content, as elaborated upon below.

Applicants now provide evidence, in the form of a Declaration from Dr. Ohno, establishing that the low-substituted hydroxypropyl cellulose (L-HPC) in the Examples of the cited '453 reference had a higher weight percentage of hydroxypropoxyl groups than that of the L-HPC component of the presently claimed solid preparations. In his Declaration, Dr. Ohno (an inventor of cited U.S. Patent No. 5,958,453) avers that the L-HPC which was used in the Examples of the '453 reference had from 10.0% to 12.9% by weight of hydroxypropoxyl groups.

Additionally, Applicants have submitted a further Declaration, of Mr. Watanabe, a Shin Etsu employee familiar with L-HPC products available at the time of the filing of the present application. Shin-Etsu was identified as a source of L-HPC in col. 5, line 24 of the cited reference. Mr. Watanabe's Declaration has been provided to illustrate the point that the L-HPC component of the presently claimed preparations was not commercially available prior to the filing of the present application. Mr. Watanabe's Declaration indicates that the lowest range of hydroxypropoxyl group content for L-HPC commercially available at the time of filing of the present application was 7.0 –9.9%.

Appendix A, attached to this amendment, further supports Mr. Watanabe's Declaration. It is a copy of a Shin-Etsu catalogue, dated February 1998, as indicated on the last page of the catalogue. On page 14, the hydroxypropoxyl contents of available L-HPC's is indicated. The lowest range available of hydroxypropoxyl group content (7.0 – 9.9%) for L-HPC commercially available at the time was found in Shin-Etsu's commercial products LH-22 and LH-32.

The evidence now provided confirms that the L-HPC component of the solid preparations of claim 1 was not known prior to the filing of the present application, so the cited reference does not anticipate claim 1. Claims 2-7, 9 and 13-17 depend upon claim 1. Applicants submit that the more specific dependent claims are also not anticipated by the cited reference for the reason provided above.

Therefore, as the '453 reference does not anticipate the presently claimed preparations, Applicants respectfully request withdrawal of the Sec. 102(b) rejection over Ohno *et al.*

VII. Discussion of the Rejection under 35 U.S.C. §103(a) over Ohno *et al.* in view of Shashoua *et al.*

Claims 1-19 have been rejected under 35 U.S.C. Sec. 103(a) for obviousness over the Ohno *et al.*, U.S. Patent No. 5,958,453 in view of Shashoua *et al.*, U.S. Patent No. 5,795,909.

The present invention is directed to a rapidly disintegrable solid preparation comprising a pharmacologically active agent, a sugar and a low-substituted hydroxypropylcellulose having 5% to less than 7% of hydroxypropoxyl groups, a method for preparing a rapidly disintegrable solid preparation and a method for improving fast disintegrability of a solid preparation. Applicants do not believe that their invention as set forth in the present claims, is taught or suggested by the combination of the cited references.

The discussion of the Ohno *et al.* reference in Sec. VI above is hereby incorporated by reference.

In addition to the argument presented above, Applicants do not believe that the specific *and lower* hydroxypropoxyl group range for the L-HPC component of the solid preparations presently claimed would be obvious from a reading of reference which utilized a higher hydroxypropoxyl group range for the L-HPC component. This is so since although the *lower* range (7.0 – 9.9 % hydroxypropoxyl group content) L-HPC was commercially available, Ohno elected to utilize L-HPC with a range of 10.0 – 12.9% hydroxypropoxyl group content. Therefore, if any trend were to have been identified by one skilled in the art, it would be that higher hydroxypropoxyl group content in the L-HPC component provided better results; not a lower hydroxypropoxyl group content, as presently claimed. Thus, the provided evidence shows that, if a trend may be identified at all, the reference (using *a higher* range than the lowest commercially available range) actually teaches away from the present invention (using *a lower* range than lowest commercially available range). Therefore, the '453 reference provides no teaching or suggestion of the L-HPC component of the presently claimed preparations and methods.

The deficiencies of Ohno *et al.* are not cured by Shashoua *et al.* The '909 reference is directed to conjugates of cis-docosahexanoic acid and taxanes. However, there is a broader

teaching in the specification that DHA may be conjugated to virtually any drug compound or diagnostic agent, as stated in col. 19, lines 62 and 63 of the cited reference. This broad statement is followed by a laundry list of exemplary compounds which is twenty-seven columns long.

The Examiner has indicated that the reference '909 has been added for the teaching of active ingredients. However, the cited reference includes active ingredients only as agents to be conjugated to DHA, for the purposes of the cited reference. There is no teaching or suggestion of non-conjugated active ingredients. Moreover, there is no teaching or suggestion in the cited reference of solid preparations of active ingredients having a sugar and L-HPC, as presently claimed.

In summary, the Ohno *et al.* reference does not disclose the L-HPC component of the presently claimed solid preparations. The Shashoua *et al.* reference does not teach the preparations of the present invention, let alone the active ingredients of the present invention. Therefore the combination of the cited references does not render the present invention obvious.

For this reason, Applicants submit that their invention, as set forth in independent claims 1, 10-12, 18 and 19 as amended, is neither taught nor suggested by the combination of the cited references. Claims 2-7, 9 and 13-17 depend upon claim 1, so Applicants submit that these more specific dependent claims are also non-obvious. Moreover, as noted above, in the present application, claim 8, directed to lansoprazole has already been cancelled. Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. Sec. 103(a) over Ohno *et al.*, U.S. Patent No. 5,958,453 in view of Shashoua *et al.*, U.S. Patent No. 5,795,909.

VIII. Discussion of Additionally Cited Art

Applicants wish to thank the Examiner for bringing the cited art of Makino *et al.* and Koyama *et al.* to their attention. Applicants have carefully reviewed these references and do not believe that they detract from the patentability of the subject invention.

IX. Conclusion

Reconsideration of the claims as amended in view of the arguments made above is solicited. Early allowance of the claims is requested. Should the Examiner believe that a conference with Applicants' attorney would advance prosecution of this application, she is respectfully requested to call Applicants' attorney.

Respectfully submitted,

Dated: January 15 EMR, 2002

Elaine M Ramesh

(847) 383-3391
(847) 383-3372

Elaine M. Ramesh, Ph.D., Reg. No. 43,032
Mark Chao, Ph.D., Reg. No. 37,293

Attorney for Applicants
Customer No. 23,115

Takeda Pharmaceuticals North America, Inc.
Intellectual Property Department
Suite 500, 475 Half Day Road
Lincolnshire, IL 60069 USA

Certificate of Mailing under 37 CFR 1.10

The undersigned hereby certifies that this document, along with any attachments, is being deposited in an envelope addressed to The Commissioner of Patents and Trademarks, with sufficient postage with the United States Postal Service EXPRESS MAIL Post Office to Addressee Service on this date January 15, 2002 .

Express Mail Label No. EL 916492483 US

Gail L. Winokur

Printed Name: Gail L. Winokur

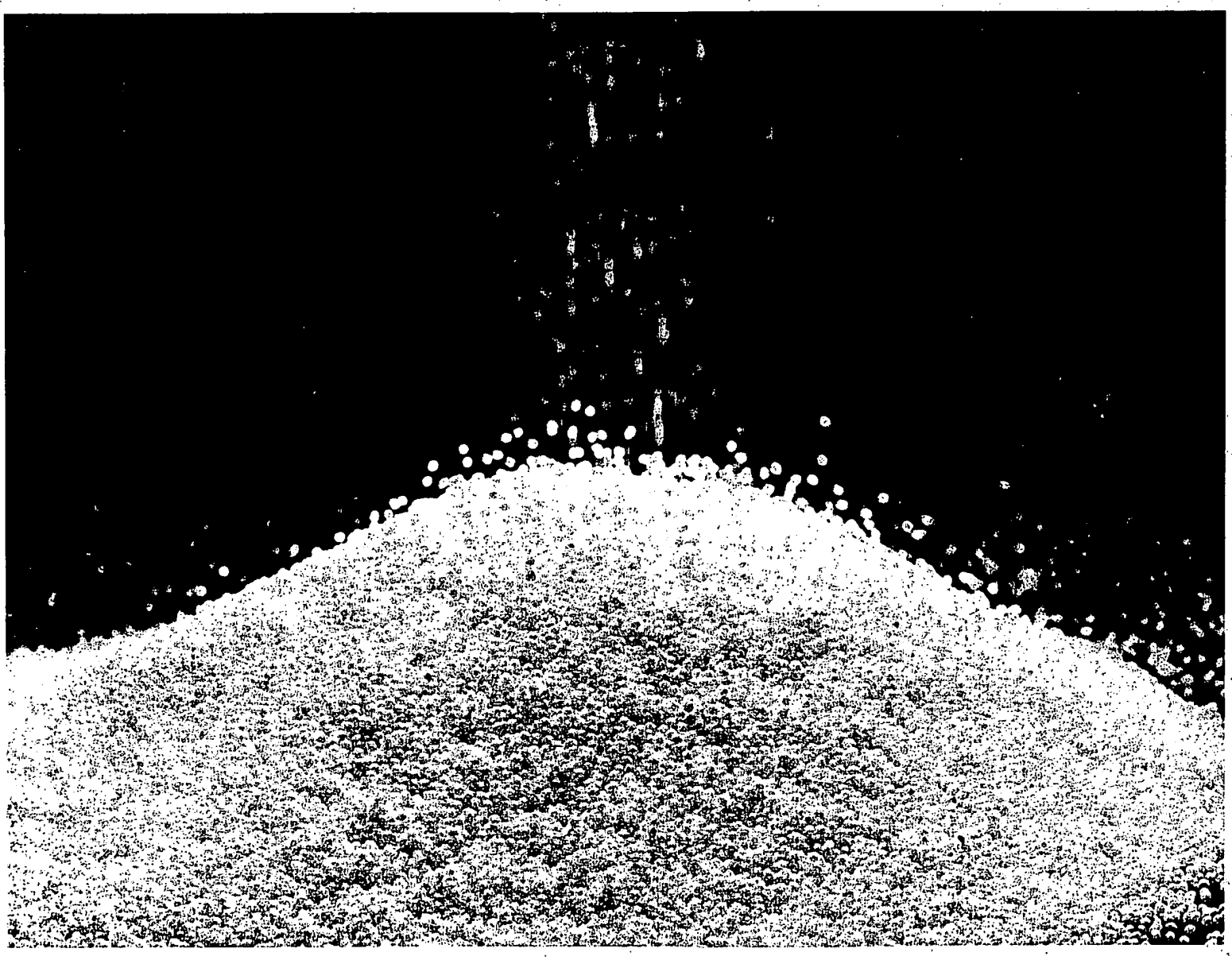
APPENDIX A

Shin-Etsu

NF
Low-Substituted Hydroxypropyl Cellulose

L-HPC

Disintegrant·Binder



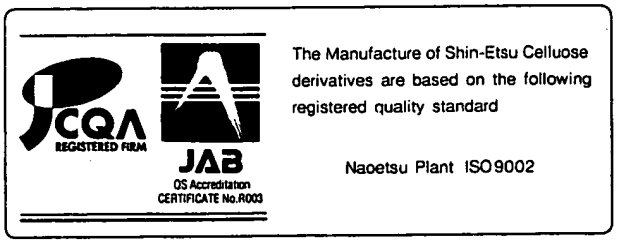
CONTENTS

PREFACE

L-HPC (Low-Substituted Hydroxypropyl Cellulose) is a low-substituted hydroxypropyl ether of cellulose in which quite a small proportion of the three hydroxyl groups contained in the ß-o-glucopyranosyl ring of the cellulose is etherified with propylene oxide. While a highly substituted (MS = 3 to 4.5) hydroxypropyl ether of cellulose is soluble in both water and alcohols, L-HPC is insoluble in these solvents but it swells in water. Moreover, modifications of the substituent content and particle size of L-HPC cause changes in the binding and the disintegrating characteristics as a result of subtle changes in physical properties. Therefore, we are manufacturing several types of L-HPC with different substituent contents and average particle sizes in order to allow the selection of the most suitable one for each type of application.

Shin-Etsu Chemical has carried out extensive research on the synthesis of numerous cellulose derivatives as well as on their application as pharmaceutical excipients. L-HPC, which has unique characteristics as a disintegrant and binder, is a product of this research and development program.

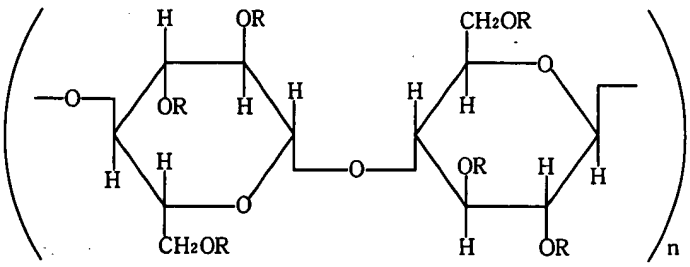
Since L-HPC was brought onto the market, its effectiveness has been confirmed by many researchers in the field of pharmaceutical technology. It was admitted to the JP XI in 1986 and also to the NF in 1990. L-HPC is manufactured in a plant controlled according to the good manufacturing practice (GMP) guidelines, and is subjected to thorough quality control testing. Furthermore, the pharmaceutical research group of Shin-Etsu Chemical is always working to improve the product, and to extend its range of applications. Technical advice is available on the suitability of L-HPC for specific applications. We are confident that L-HPC will be a widely useful, pharmaceutical material, offering a simplified preparation composition, an improvement in drug bioavailability and a highly stable drug formulation.



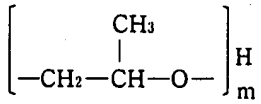
DESIGNATION AND STRUCTURAL FORMULA OF L-HPC

Designation	Low-Substituted Hydroxypropyl Cellulose (L-HPC)
Admissions to compendia	NF, JP
Chemical name	Cellulose, 2-hydroxypropyl ether (low-substituted) (CAS 9004-64-2)
Trade name	L-HPC

Structural formula



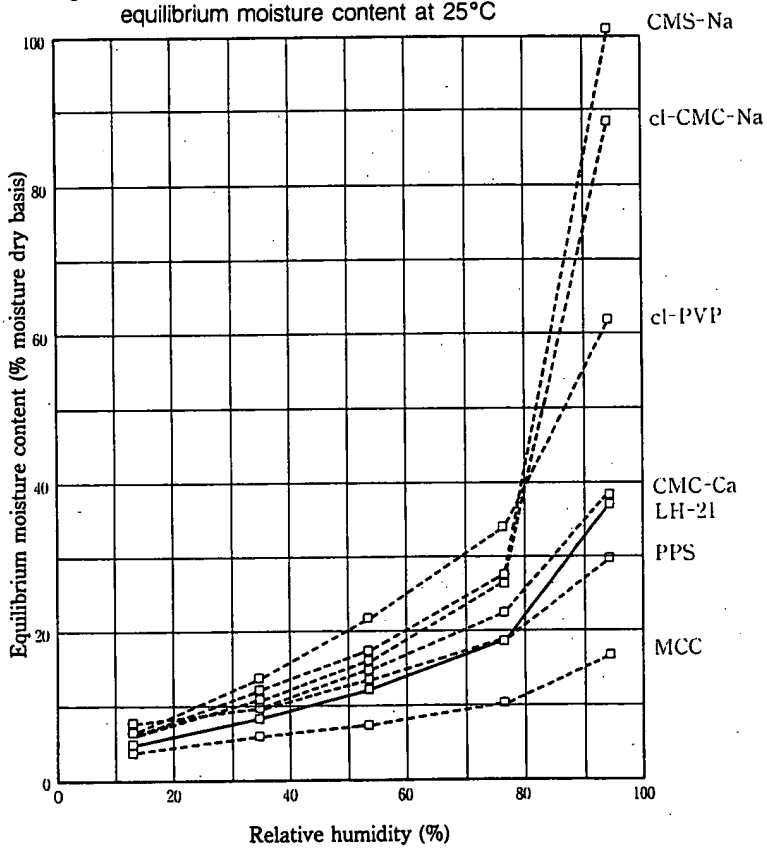
R=H or



PHYSICO-CHEMICAL PROPERTIES OF L-HPC

1) Real specific gravity ·····1.46
2) Apparent density·····0.45～0.70 g/mL(tapped)
(differs by type)
3) Equilibrium moisture content·····
The relationship between relative humidity and equilibrium moisture content of L-HPC, various disintegrants and microcrystalline cellulose is shown in Fig. 1. The data for LH-21, a representative type of L-HPC, are shown; other types, of L-HPC show similar relationships.

Fig. 1: Relationship between relative humidity and equilibrium moisture content at 25°C



Abbreviations are as follows

CMS-Na	Sodium carboxymethyl starch
cl-CMC-Na	Cross-linked sodium carboxymethylcellulose
cl-PVP	Cross-linked polyvinylpyrrolidone
CMC-Ca	Calcium carboxymethylcellulose
PPS	Partly pregelatinized starch
MCC	Microcrystalline cellulose

4) Solubility

L-HPC does not dissolve in water but swells. It neither dissolves nor swells in ordinary organic solvents, but dissolves in a 10% NaOH solution to give a viscous solution.

Table 1: Solubility of L-HPC

Solvent	Solvent required to dissolve 1 g of L-HPC	State
10% NaOH soln.	9mL	Viscous solution
10% Na_2CO_3 soln.	More than 10,000 mL	Swollen
Water 2 N HCl		
Ethanol Ethyl ether		Insoluble

5) Types of L-HPC and their powder properties

As shown in Table 2, the types of L-HPC comprise various combinations of average particle size and hydroxypropoxyl content.

Table 2: Types of L-HPC

	low ——— Hydroxypropoxyl content ——— high		
Particle size fine — coarse		LH-11	
	LH-22	LH-21	LH-20
	LH-32	LH-31	LH-30

Typical powder properties of the seven types of L-HPC currently available are shown in Table 3.

Table 3: Powder properties of each type of L-HPC

Type		LH-11	LH-21	LH-31	LH-22	LH-32	LH-20	LH-30
Bulk density Loose	g/mL	0.34	0.40	0.30	0.37	0.21	0.36	0.25
Bulk density Tapped	g/mL	0.57	0.65	0.59	0.63	0.49	0.65	0.51
Angle of repose	degrees	49	45	49	48	53	48	51
Average particle size	μm*	50	40	25	40	25	40	25

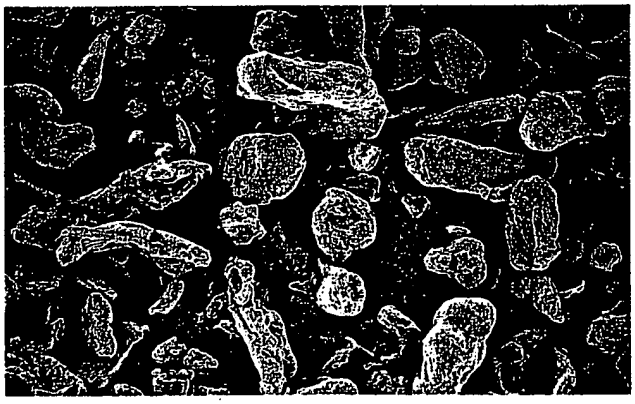
*Expressed as the values extrapolated on Rosin Rammler chart for the particle size distribution, which was obtained by sieving using a Ro-tap testing sieve apparatus.

6) Electron micrographs

LH-11

LH-21

LH-31



10μm

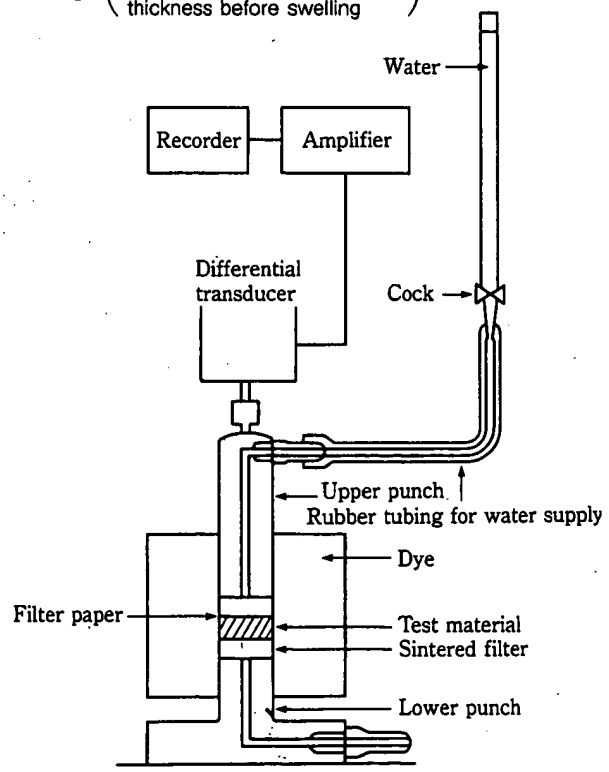
7) Swelling properties

The swelling properties of L-HPC, as a measure of its disintegrant ability, were measured using the equipment illustrated in Fig. 2. In general, the swelling properties of a disintegrant depend on the nature of the drug, the diluting substance, the binder, etc. In this experiment the swelling was measured by compressing tablets composed of alumina, which does not swell in water, as a base. The upper punch was then replaced immediately with a punch fitted with a water supply tube. The results of a comparison of the swelling properties between L-HPC and various disintegrants and binders as well as swelling of the various types of L-HPC are presented below.

Composition of tablet and conditions of tableting		
Composition	Disintegrant or binder	100 mg
	Alumina	400 mg
	Total	500 mg/tablet
Tableting pressure		55MPa
Tablet shape		15 mmϕ flat

Fig. 2: Apparatus for measuring degree of swelling

$$\text{Degree of swelling} = \left(\frac{\text{thickness after swelling}}{\text{thickness before swelling}} - 1 \right) \times 100$$



a) Swelling properties of L-HPC and various disintegrants and binders

Fig. 3 shows the swelling properties of L-HPC and various disintegrants and binders. Swelling of L-HPC reaches saturation in a short time, and L-HPC is considered to be readily wettable. Moreover, among those disintegrants for which swelling reaches saturation within 60 seconds, L-HPC exhibits the greatest degree of swelling.

b) Types of L-HPC and their swelling properties

Fig. 4 illustrates the swelling properties of the various types of L-HPC.

The relationship between average particle size and degree of swelling of L-HPC after 60 seconds, is shown in Fig. 5. The types with a larger average particle size have a higher degree of swelling. In addition, as regards the relationship between the hydroxypropoxyl content and the degree of swelling, LH-20 and LH-30 with a high hydroxypropoxyl content tend to need a longer time for the swelling to reach saturation compared with the other types. Comparisons of the degree of swelling between LH-21 and LH-22 or between LH-31 and LH-32 demonstrate that LH-21 and LH-31 with a higher hydroxypropoxyl content show higher degrees of swelling, respectively.

Fig. 3: Swelling properties of L-HPC and various disintegrants and binders

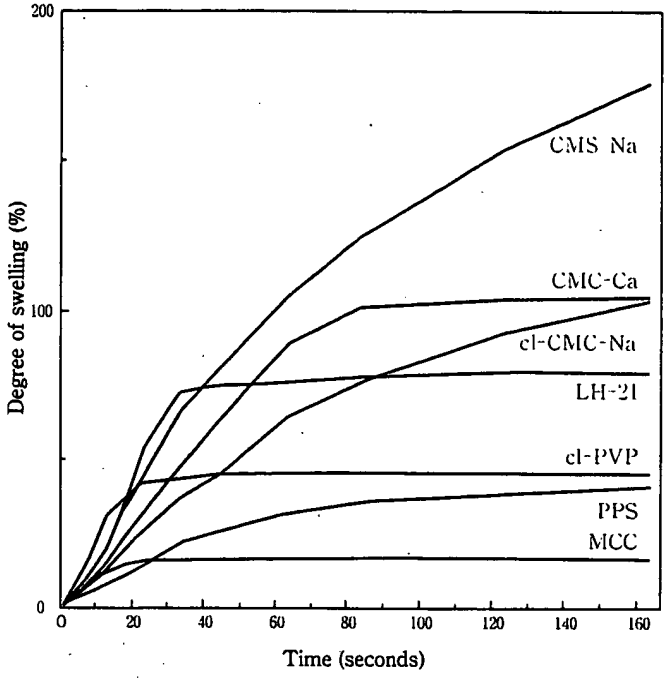
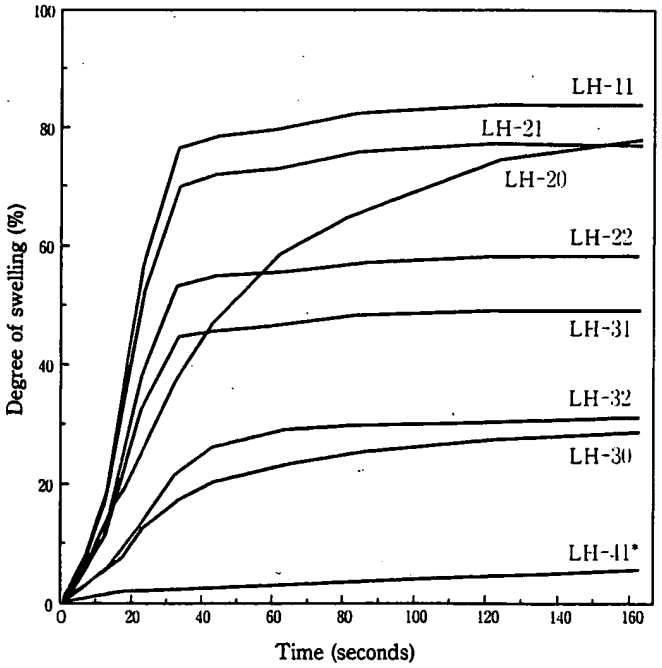
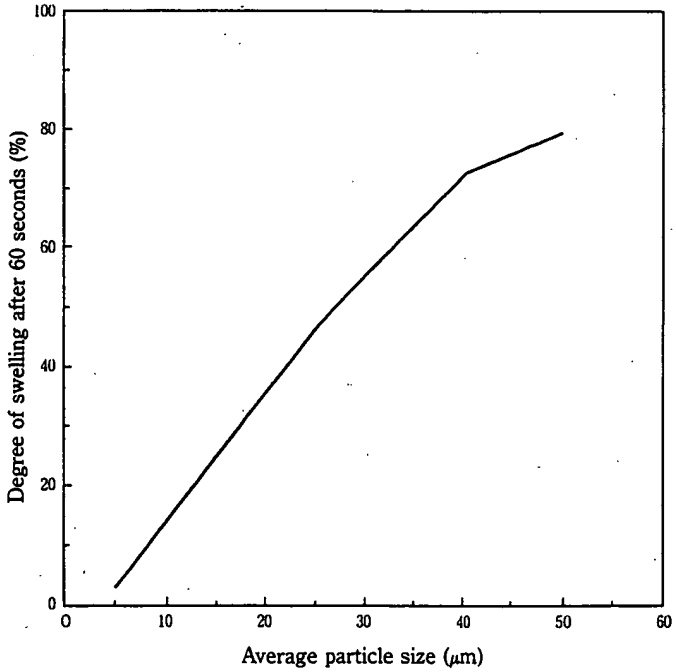


Fig. 4: Swelling properties of various types of L-HPC



*Trial product (L-HPC ultrafine particles)

Fig. 5: Average particle size and degree of swelling of L-HPC



BASIC CHARACTERISTICS OF PREPARATIONS CONTAINING L-HPC

1) Disintegration and binding characteristics

L-HPC has a binding ability as well as a swelling characteristic as a disintegrant. In order to evaluate the disintegration and binding characteristics, a tableting test using spray-dried lactose as a base was performed. The disintegration time and the tablet hardness of L-HPC and various disintegrants and binders were compared. Furthermore, the characteristics of different types of L-HPC were also comparatively studied. The results are presented below.

a) Comparison of disintegration time and tablet hardness between L-HPC and various disintegrants and binders

The disintegration time and tablet hardness of L-HPC (represented by LH-21) and various disintegrants and binders are shown in Fig. 6. L-HPC has a shorter disintegration time than the other disintegrants and binders, and the tablet hardness of L-HPC was the fourth highest suggesting that this base has a good combination of disintegration and binding properties.

Test methods

Tablet composition ·····	Spray-dried lactose*	159.2 mg
	Binder or disintegrant	39.8 mg
	Magnesium stearate	1.0 mg
	Total	200.0 mg/tablet

(*: Fast-Flo lactose)

Preparation ·····Spray-dried lactose / Binder or disintegrant

→ Mixing (5 L V-blender, 20 min)

→ Magnesium stearate

→ Mixing (5 L V-blender, 2 min)

→ Tableting (Rotary tableting machine, HT-P18)

Rotational speed: 30 min^{-1}

Punch: 8 mmϕ. 6.5 mmR

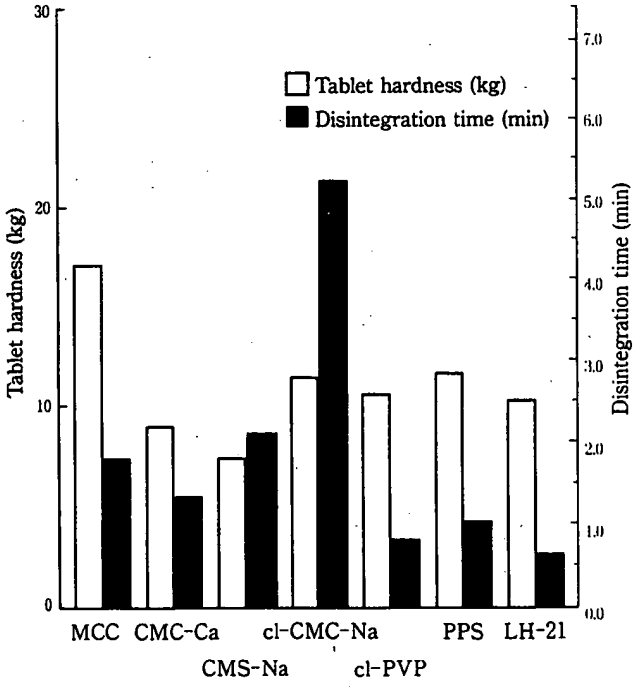
Tableting pressure: 1st pressure : 59 MPa

2nd pressure : 195 MPa

Measurement ·····Tablet hardness : Erweka hardness tester

Disintegration time : USP disintegration test

Fig. 6: Disintegration time and tablet hardness of L-HPC and various disintegrants and binders



b) Comparison of disintegration time and tablet hardness between types of L-HPC

The disintegration time and the tablet hardness of various types of L-HPC are shown in Fig. 7. There is a tendency for L-HPC with a larger average particle size to have a shorter disintegration time and for L-HPC with a smaller average particle size to have a higher hardness. The relationships among the average particle size, disintegration time and tablet hardness of L-HPC are presented in Fig. 8. In this experiment, L-HPC containing 10.0 ~ 12.9% hydroxypropoxyl content was used.

Fig. 7: Comparison of disintegration time and tablet hardness of different types of L-HPC

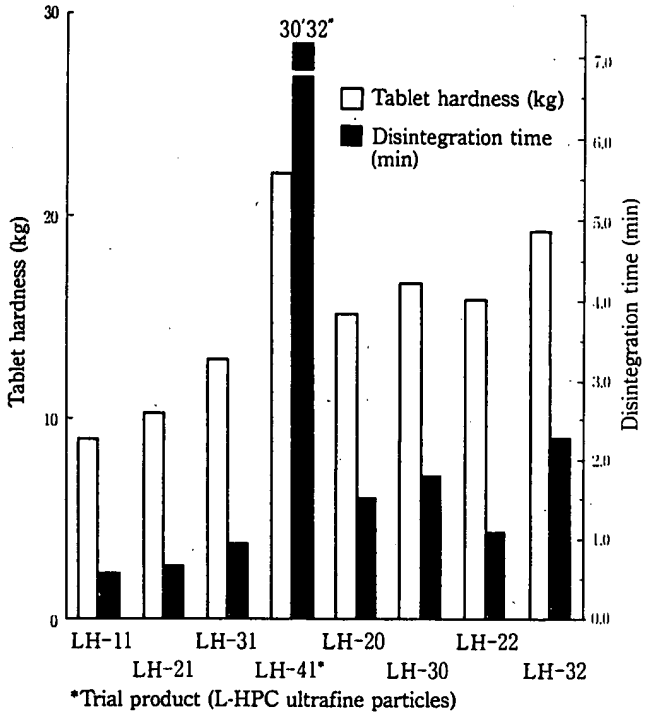
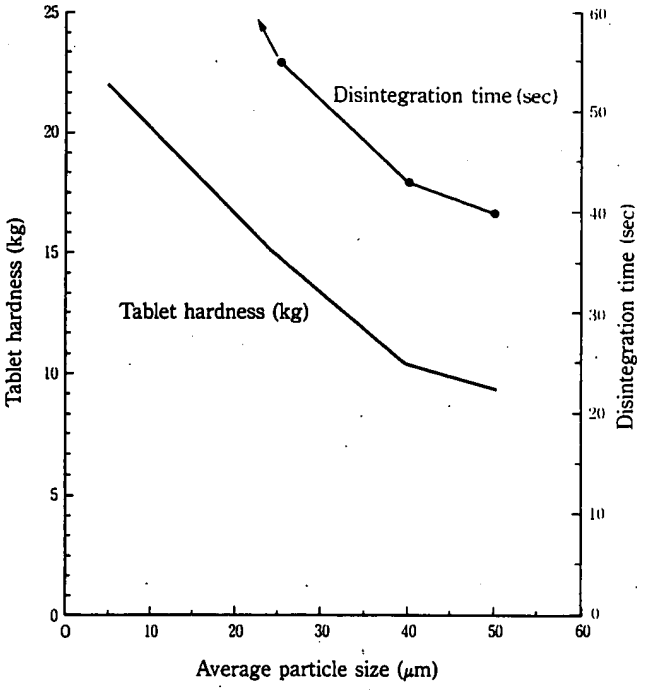


Fig. 8: Dependence of the disintegration time and tablet hardness of compressed tablets, on the average particle size of L-HPC



c) Comparison of tablet stability between L-HPC and various disintegrants and binders

The tablet prepared in a) were allowed to stand at 50°C, and at 40°C, 75% RH to test the stability of hardness, disintegration time and coloring (YI). L-HPC was a stable excipient with little change in any category. Fig 9 illustrates the changes in tablet hardness, disintegration time and YI during storage at 50°C. Fig. 10 shows the corresponding changes during storage at 40°C, 75% RH. Abbreviations are as given in Fig. 1.

Fig. 9: Changes in tablet hardness, disintegration time and YI during

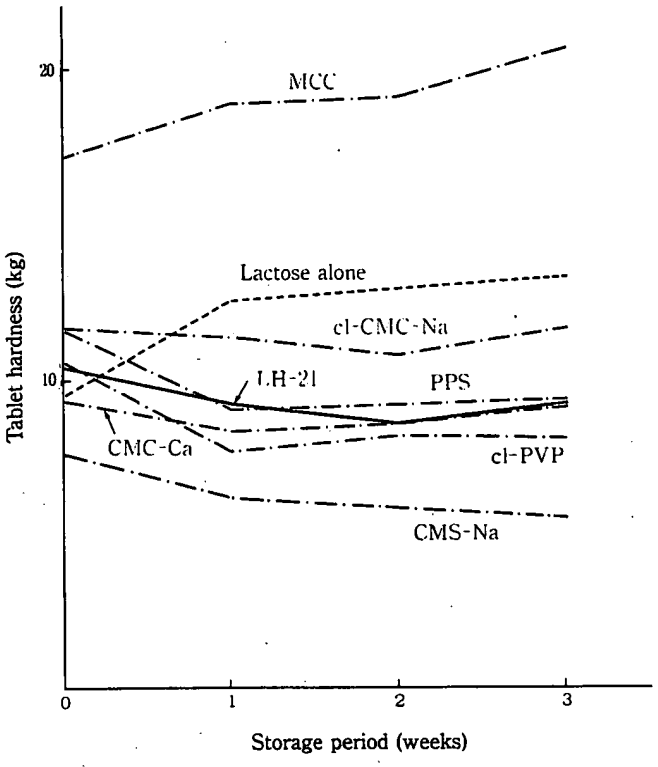
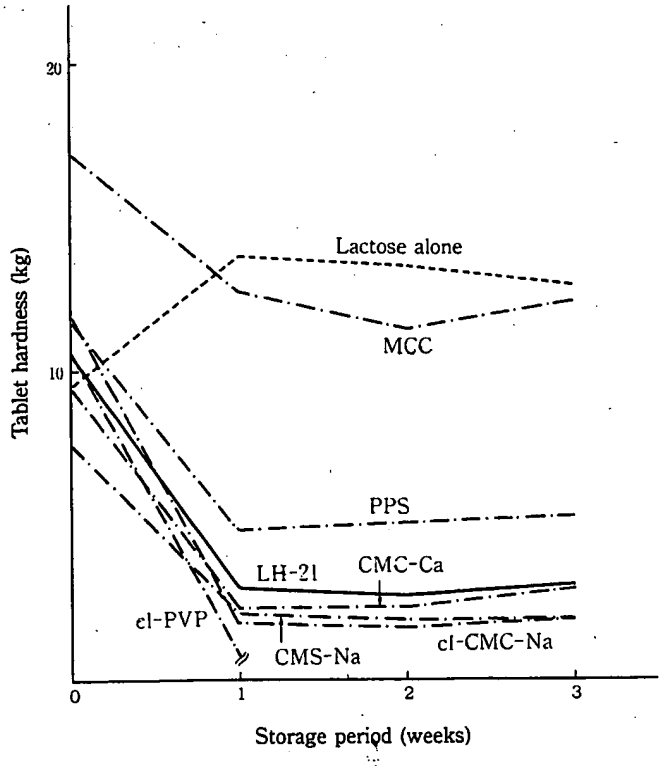
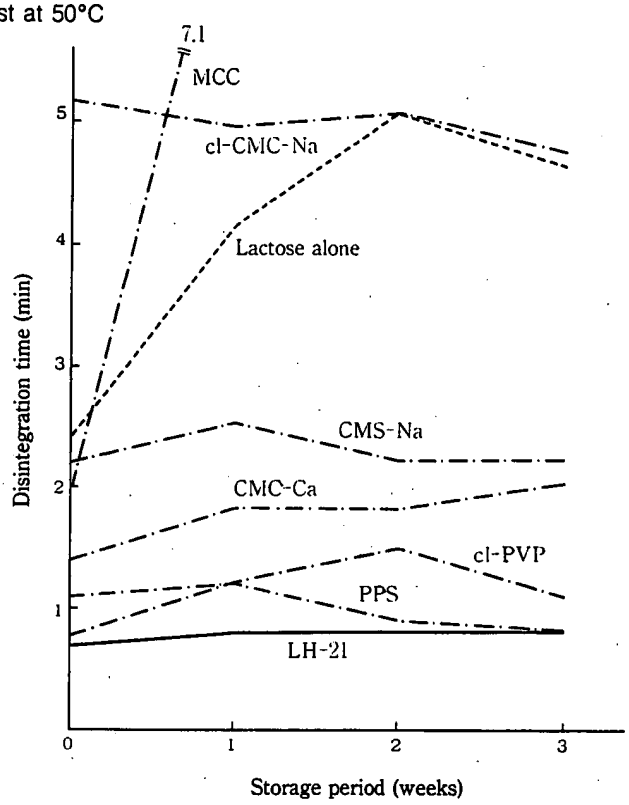
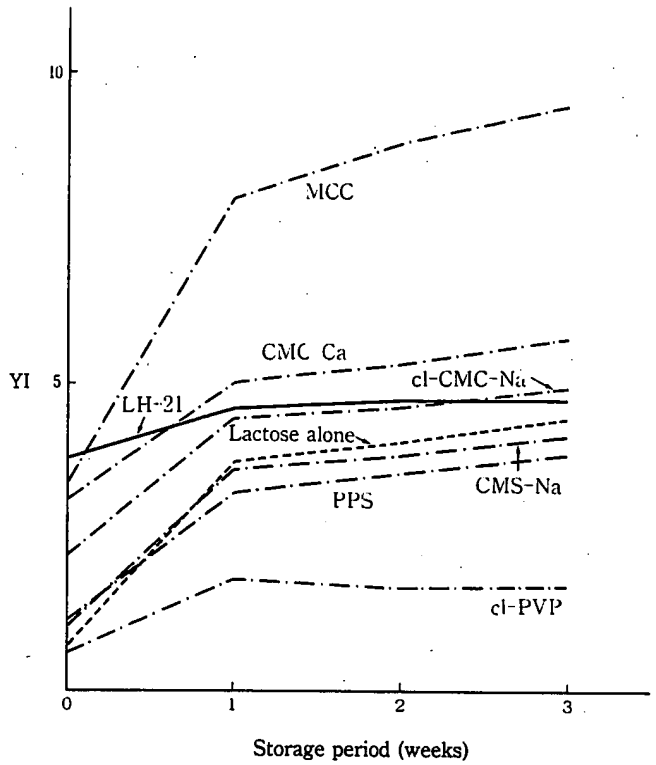


Fig. 10: Changes in tablet hardness, disintegration time and YI durir

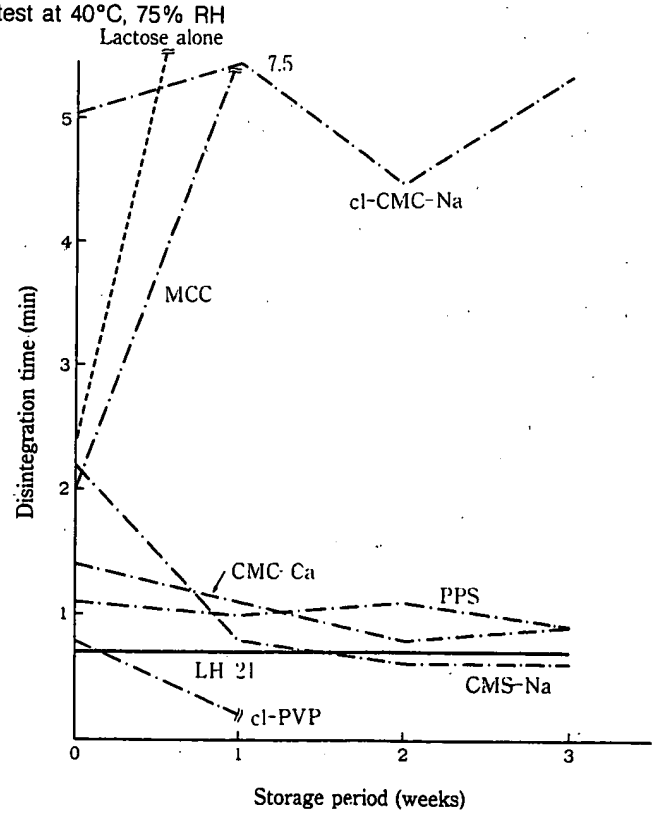


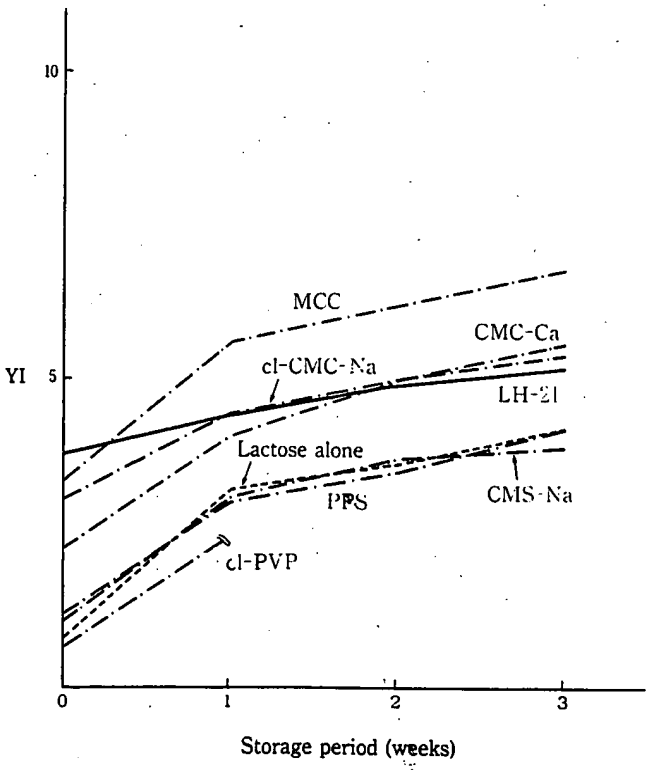
age test at 50°C





age test at 40°C, 75% RH





2) Ability to prevent capping

L-HPC, particularly LH-11, is a useful excipient to prevent capping during tableting. This is probably because the powder of LH-11 is composed of fibrous particles which form an interlocking network in a tablet. Fig. 11 and Fig. 12 illustrate the dependence of capping occurrence and tablet hardness on the type of L-HPC used.

Test method

Tablet composition

Phenacetin	84.0 mg
Lactose	179.2 mg
L-HPC	14.0 mg
Magnesium stearate	1.4 mg
Talc	1.4 mg
Total	280.0 mg/tablet

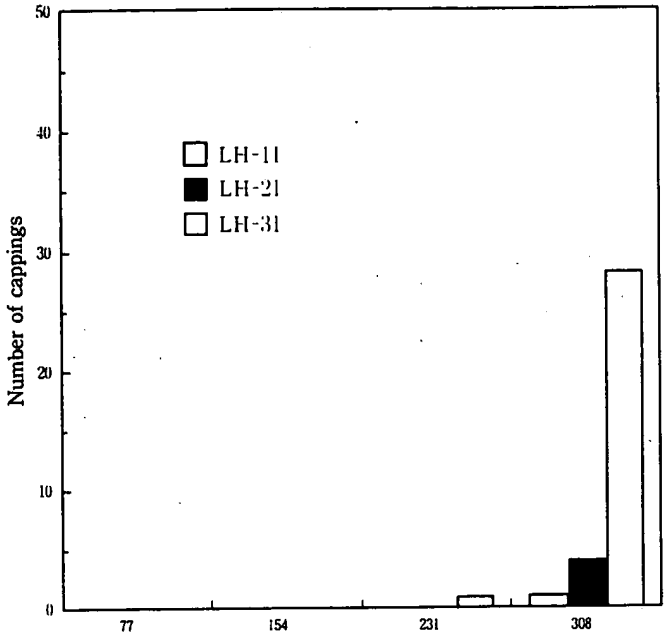
Preparation

- Phenacetin, Lactose, L-HPC
- Mixing (10 L Henschel mixer, 20 sec)
  - Water
- Wet massing (10 L Hanschel mixer, 2 min)
- Granulation (Sieve No. 20)
- Drying (60°C, Oven)
- Sieving (Sieve No. 18)
  - Mixture of magnesium stearate and talc
- Mixing (5 L V-blender)
- Tableting (Rotary tableting machine HT-P18)
  - Rotational speed: 40 min^{-1}
  - Punch: 9 mmϕ. 7.5mmR

Measurement

- Capping : Roche Friabilator
  50 tablets, 25 min^{-1}, 30 min
- Tablet hardness : Erweka hardness tester

Fig. 11: Relationship between capping occurrence and the type of L-HPC used



3) Granulation of kneaded products

Because of its ability to absorb water and to swell, L-HPC can extend the range of allowable amount of water added during the granulation of a non-wettable drug where a moderate kneading state can be obtained.

Fig. 13 shows the relationship between the water content during kneading and the granulation velocity for various types of L-HPC. A type with a higher hydroxypropoxyl content has a higher granulation velocity, though small changes in the granulation velocity due to changes in the water content are apparent. Moreover, a smaller average particle size results in an increase of the granulation velocity.

Test method

Kneaded product composition ..... Phenacetin 90 parts
L-HPC 10 parts
Total 100 parts

Kneading and granulating method .....

Phenacetin L-HPC
↓
Mixing (10 L Henschel mixer, 30 sec)
← Water
↓
Kneading (10 L Henschel mixer, 3 min)
↓
Granulation (5″ Cylindrical granulator)
Screen pore diameter: 0.6 mm

Fig. 12: Relationship between tablet hardness and type of L-HPC used

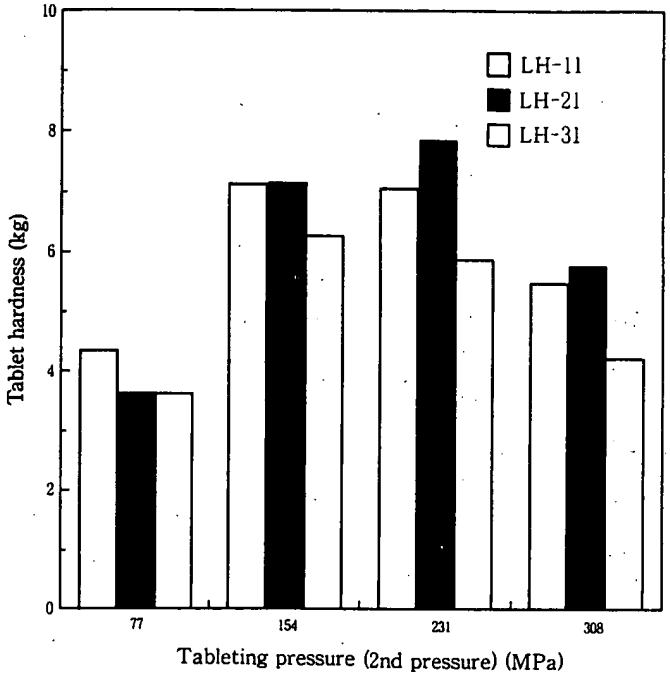
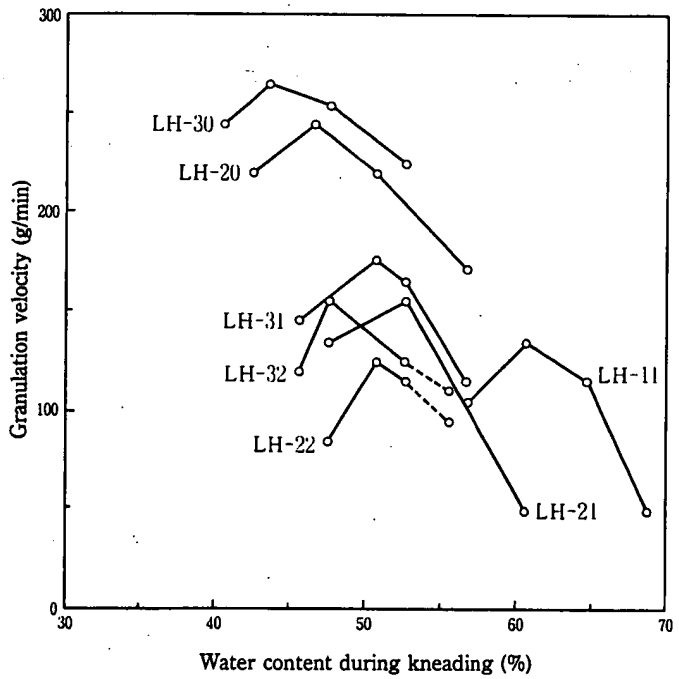


Fig. 13: Relationship of water content during kneading and granulation velocity for various grades of L-HPC



Granulation velocity is given on a dry weight basis.

SPECIFICATIONS AND TEST METHODS OF L-HPC

The quality specifications for L-HPC are listed in Table 4. L-HPC is an NF Low-Substituted Hydroxypropyl Cellulose. The specifications and test methods are based on the NF monograph. Moreover, the packaging of the products is labeled "For Manufacturing, Processing or Repacking".
Shin-Etsu Chemical performs strict quality control tests to meet GMP regulations, such as the foreign matter tests, the yellowness index test and the microbiological tests.

Table 4: Quality specifications for L-HPC

Item \ Type	LH-11	LH-20	LH-21	LH-22	LH-30	LH-31	LH-32	Method
1. Description and Solubility	conforms							USP/NF
2. Identification A: B: C:	conforms							USP/NF
3. pH	5.0~7.5							JP
4. Loss on drying	not more than 5.0%							USP/NF
5. Residue on ignition	not more than 0.5%							USP/NF
6. Chloride	within the limit (not more than 0.36%)							USP/NF
7. Arsenic	within the limit (not more than 2 ppm)							USP/NF
8. Heavy metals	within the limit (not more than 0.001%)							USP/NF
9. Hydroxypropoxyl content	10.0~12.9%	13.0~16.0%	10.0~12.9%	7.0~9.9%	13.0~16.0%	10.0~12.9%	7.0~9.9%	USP/NF
10. Particle size	180 μm on: not more than 0.5% 150 μm pass: not less than 98%	106 μm on: not more than 1.0% 75 μm pass: not less than 90%			75 μm on: not more than 5.0% 45 μm pass: not less than 50%			Ro-tap sieve method

*Items 3,7 and 10 are not required by the USP/NF monograph, but are tested according to the mentioned methods as Shin-Etsu specifications.

Although great care is taken to avoid any foreign material contamination, it is recommended to sieve the product before usage.

APPLICATIONS OF L-HPC

1) Application to tableting

a) Tableting by the direct compression method

Multi-vitamin tablets are generally manufactured by the wet granulation method but changing to the direct compression method is expected to reduce the manufacturing cost.

Here, an example of application of the direct compression method to the manufacture of multi-vitamin tablets in shown.

Table 5: Tablet composition

	Active Ingredients	Content per tablet	Composition per tablet	Composition of batch
Master batch	1) Vitamin A (dry, stabilized form)	Vitamin A: 5000 IU	2.0 mg	20.0 g
	2) Vitamin AD (dry, stabilized form)	Vitamin D: 400 IU	8.0 mg	80.0 g
	3] Vitamin E (dry, stabilized form)	15 IU	60.0 mg	600.0 g
	4) Folic acid	0.4 mg	0.4 mg	4.0 g
	5) Thiamine nitrate	1.5 mg	1.5 mg	15.0 g
	6) Riboflavin	1.7 mg	1.7 mg	17.0 g
	7) Nicotinic acid	20.0 mg	20.0 mg	200.0 g
	8) Vitamin B_6	2.0 mg	2.0 mg	20.0 g
	9) Vitamin B_{12}	6 μg	0.6 mg*	6.0 g
	Subtotal		96.2 mg	962.0 g
Mixing of tableting	Master Batch	500 mg	96.2 mg	96.2 g
	10) Vitamin C granules		515.0 mg	515.0 g
	11) LH-11		30.6 mg	30.6 g
	12) Spray-dried lactose		249.2 mg	249.2 g
	13) Magnesium stearate		9.0 mg	9.0 g
	Total		900.0 mg/tablet	900.0 g

*A 100-times-diluted mixture with lactose was used.

Manufacturing method

●Manufacture of master batch

Drug powder items 3 ~ 9
↓
Mixing (5 L V-blender, 40 min^{-1}, 3 min)
↓
Sieving (Sieve No. 25)
↓
Mixing (10 L Henschel mixer, 1 min)
↓
Sieving (Sieve No. 25)
↓
Drug powder items 1 and 2 —
↓
Mixing (5 L V-blender, 40 min^{-1}, 3 min)
↓
Sieving (Sieve No. 25)
↓
Master batch

●Manufacture of tableting powder

Master batch
↓
Items 10 ~ 12
↓
Mixing (5 L V-blender, 40 min^{-1}, 3 min)
↓
Sieving (Sieve No. 25)
↓
Mixing (5 L V-blender, 40 min^{-1}, 20 min)
↓
Magnesium stearate —
↓
Mixing (5 L V-blender, 40 min^{-1}, 2 min)
↓
Tableting (Rotary tableting machine HT-P18)
Rotational speed: 30 min^{-1}
Punch: Oblong 17.8 mm × 7.8 mm
Tableting pressure: 1st pressure: 71MPa
2nd pressure: 212MPa

Table 6: Tablet properties

Tablet hardness	19.6 kg
Tablet thickness	5.80 mm
Disintegration time	23 min 16 sec
Friability	0.22%

●Measurement:
Tablet hardness: Monsanto hardness tester (measurement in the direction of long diameter)
Tablet thickness: Dial gauge
Disintegration time: Apparatus for USP disintegration test
Friability: Roche Friabilator (20 tablets, 25min^{-1}, 4 min)

Multi-vitamin tablets manufactured experimentally by the direct compression method showed properties similar to those of commercially available products.

b) Tableting by the wet granulation method

As an application of L-HPC to a preparation with a high drug content, we present an application to tableting by the wet granulation method for acetaminophen. Because of its swelling property in water, L-HPC functions to form granules for tableting without the use of a water-soluble binder paste solution.

Table 7: Tablet composition

	Tablet composition	Composition of batch
Acetaminophen	501.5 mg	858.6 g
LH-11	82.6 mg	141.4 g
Magnesium stearate	2.95 mg	3.3 g
Talc	2.95 mg	3.3 g
Total	590.0 mg/tablet	1006.6 g

Manufacturing method

Acetaminophen, L-HPC

↓

Mixing (10 L Henschel mixer, 30 sec)

← Water

↓

Wet massing (10 L Henschel mixer, 3 min)

↓

Granulation (Sieve No. 18)

↓

Drying (60°C, Oven)

↓

Sieving (Sieve No. 20)

← Magnesium stearate/Talc = 1/1 mixture powder

↓

Mixing (5 L V-blender, 2 min)

↓

Tableting (Rotary tableting machine, HT-P18)

Rotational speed: 30 min^{-1}

Punch: 13 mmϕ flat

Tableting pressure: 1st pressure : 37MPa

2nd pressure: 111MPa

Table 8: Tablet characteristics

Tablet hardness	6.1 kg
Disintegration time	22 sec

- Measurement:
  Tablet hardness: Erweka hardness tester
  Disintegration time: Apparatus for USP disintegration test (37°C, water)

2) Application to granules

In this experiment, L-HPC was applied to prepare granules containing acetaminophen, ethenzamide and caffeine using a cylindrical granulator.

Table 9: Granule composition

	A	B
Acetaminophen	352.0 mg	352.0 mg
Ethenzamide	160.0 mg	160.0 mg
Caffein	48.0 mg	48.0 mg
Lactose	73.5 mg	73.5 mg
Cornstarch	31.5 mg	31.5 mg
LH-20	35.0 mg	21.0 mg
PHARMACOAT-606		14.0 mg
Total	700.0 mg	700.0 mg
Water content during kneading	25.7 %	20.0 %

Manufacturing method

Drugs L-HPC (Charge 1.5 kg)

↓

Mixing (20 L Supermixer, 30 sec)

← Water

↓

Kneading (20 L Supermixer, 30 sec)

↓

Granulation (5″ Cylindrical granulator)

↓

Drying (60°C, Oven)

↓

Sieving (Sieve No. 20)

↓

Classification (Sieve No. 20～45)

Table 10: Granule characteristics

	A	B
Granulation velocity	225 g/min	290 g/min
Granule strength	0.46 %	0.13 %
Disintegration time	100～110 sec	45～50 sec

●Measurement

Granule strength: Roche friabilator
10 g, 25 min^{-1}, 10 min
The rate in which powder passed through sieve No. 50 was calculated.

Disintegration time: Apparatus for USP disintegration test

In every case, satisfactory granule properties were obtained. Although the addition of L-HPC alone is adequate, combination with a water-soluble binder further improves the properties.

3) Stability of aspirin tablets

In order to study the effect of L-HPC on the stability of drugs, L-HPC was used to prepare aspirin tablets. The salicylic acid content was investigated during storage tests.

Table 11. Tablet composition and initial tablet characteristics

		A	B
Composition	Aspirin granular powder	267 mg	267 mg
	LH-11	30 mg	...
	Cornstarch	...	30 mg
	Talc	3 mg	3 mg
	Total	300 mg/tablet	300 mg/tablet
Characteristics	Tablet hardness	12.3 kg	9.0 kg
	Disintegration time	1 min 26 sec	35 min 20 sec
	Friability	0.58 %	0.68 %
	Aspirin content	267.4 mg/tablet	268.5 mg/tablet
	Salicylic acid content	0.2 mg/tablet	0.2 mg/tablet

Manufacturing method

Aspirin granular powder — L-HPC or cornstarch

↓ Mixing (5 L V-blender, 3 min)

↓ Sieving (Sieve No.50)

↓ Mixing (5 L V-blender, 10 min)

Talc

↓ Mixing (5 L V-blender, 3 min)

↓ Tableting (Rotary tableting machine, HT-P18)

Rotational speed: 30 min^{-1},

Punch: 9 mmϕ, 7.5mmR

Tableting pressure: 1st pressure : 77MPa

2nd pressure : 154MPa

Measurement:
Tablet hardness: Monsanto hardness tester
Disintegration time: Apparatus for USP disintegration test
Friability rate: Roche friabilator, 20 tablets, 25 min^{-1}, 4 min
Determination of aspirin and salicylic acid:
The contents were determined by spectrophotometry according to R.B. Tinker et al.
[J. Am. Pharm. Assoc., Sci Ed. 315 (1954)].

Table 12: Results of stability test

Storage conditions	Room temperature, Tightly stoppered, 6 months		40°C, 75% RH, One month	
	A	B	A	B
Tablet hardness	9.8 kg	10.3 kg	8.8 kg	11.8 kg
Disintegration time	1 min 15 sec	35 min 20 sec	1 min 20 sec	3 min 25 sec
Friability	0.72 %	0.95 %	0.96 %	1.06 %
Aspirin content	267.1 mg/tablet	268.0 mg/tablet	265.3 mg/tablet	266.1 mg/tablet
Salicylic acid content	0.4 mg/tablet	0.3 mg/tablet	0.9 mg/tablet	0.8 mg/tablet

L-HPC was found not to have any adverse effect upon the stability of aspirin.

PACKAGING, SUGGETIONS FOR SELECTING TYPES OF L-HPC

50kg net : double layered polyethylene bag in fiber drum
- 1 kg net : double layered polyethylene bag

Type	Usage	Purpose
LH-11	Tablets	Improvement in binding properties (prevention of capping) Improvement in disintegrating properties
LH-22	Tablets•Granules	Improvement in disintegrating and binding properties of preparations containing hydrophilic drugs
LH-21	Tablets•Granules	Improvement in disintegrating and binding properties of preparations containing hydrophobic drugs
LH-20	Granules	Improvement in granulating and disintegration properties
LH-32	Tablets•Granules	Improvement in disintegrating and binding properties of hydrophilic drugs
LH-31	Tablets•Granules	Improvement in disintegrating and binding properties of hydrophobic drugs
LH-30	Granules	Improvement in granulating and disintegrating properties

Careful work practice are important for the safe handling of this material. Read and understand the Material Safety Data Sheet before using L-HPC.

PRECAUTIONS IN HANDLING

1) Warning : May Form Flammable or Explosive Dust-Air Mixtures.

When handling in large quantities or in bulk, take precautions to avoid accumulation and suspension of dust in the air. Keep Away from Heat, Sparks and Flame. Do not Permit Grinding, Welding, Drilling or Smoking near this Material. General precautions outlined in the National Fire Protection Association's NFPA 63 "Prevention of Dust Explosions in Industrial Plants" and NFPA 654 "Standard for the Prevention of Dust Explosions in the Plastics Industry" are recommended.

2) Caution : May Cause Eye Irritation

Avoid contact with eyes, skin and clothing.
Wash thoroughly after handling. Wash contaminated clothing before re-use. Use only with adequate exhaust ventilation. Follow an organized housekeeping plan. Keep floors and equipment clean.

3) Emergency and First Aid Procedures

If Ignited : Extinguish the fire with a common fire extinguisher.
If Inhaled : Remove the affected person to fresh air. Give artificial respiration if breathing stops. Get immediate medical attention. (A dust mask should be worn for handling a large quantity).
In Case of Eye Contact : Flush eyes with water for at least 15 minutes while holding eyelids open. Get immediate medical attention.
In Case of Skin Contact : Wash off with flowing water.

4) In Case of Material Spills and Leakage

The following steps should be taken.

- Wear an approved respirator, rubber gloves, rubber boots and safety goggles.
- Vacuum or sweep up spillage. Prevent dust generation. Place spillage in an appropriate container for waste disposal.
- Ventilate area and wash spill site.
- Wash contaminated clothing before re-use.

5) Storage

Keep dry. Store away from heat and sunlight. Store in sealed containers.

6) Disposal

Contents : Dispose of unused contents in accordance with all applicable Federal, State and local laws. Consult the distributor for further information.
Container : Do not re-use container. Dispose of empty container by the procedures approved by Federal, State and local authorities.

Carefully read and understand the Material Safety Data Sheet (MSDS) before using this product.

The information contained in this brochure does not constitute an express or implied warranty of quality. Any warranty of merchantability or fitness for a particular purpose is hereby disclaimed.

Cellulose & Pharmaceutical Excipients Department
Asahi-Tokai Building
6-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo, Japan
TEL : 81-3-3246-5261 FAX : 81-3-3246-5372
Cable Address : KAGAKUSHINETSU TOKYO

Revised 98.2 98.2/1,000